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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,372	ADEMA, ENNO	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-11* is/are pending in the application.

4a) Of the above claim(s) *3 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/18/2009 has been entered.

2. Claims 1, 4, 6, 8, and 10-11 were amended. Claim 2 was canceled. Accordingly, claims 1 and 3-11 are pending in the application, with claims 3 and 5 currently withdrawn. Claims 1, 4, and 6-11 are subject to examination below.

Priority

3. The present application was filed on 8/29/2003 and claims foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 102 39 821.6, filed on 8/29/2002 in Germany.

Objections/ Rejections Withdrawn

4. The rejections under § 112, 1st paragraph as containing new matter have been withdrawn in response to Applicant's amendments. However, the claims remain rejected under this statute as set forth below (written description).

5. The rejections under § 112, 2nd paragraph as set forth in the previous Office action have been withdrawn in response to Applicant's amendments.

6. The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. in view of Furatu, Morris et al., Akhavan-Tafti et al. and Nesheim et al (US 5,308,755) has been withdrawn in response to Applicant's amendments to the claim to specify that the third reagent R3 comprises additional thrombin.

Specification

7. The use of the trademark Polybrene® has been noted in this application (see, e.g., [0013]). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4, and 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Written Description

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter

later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...") *Regents of the University of California v. Eli Lilly & Co,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a

representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims recite a method for detecting antithrombin III (AT) in a sample that may contain one or more pharamaceutical compounds that inhibit thrombin (i.e., thrombin inhibitors) using three reagents, R1, R2, and R3. The claim further states that R1 comprises thrombin.

However, the claimed reagents R2 and R3 encompass a genus of molecules not adequately described by the specification. Dependent claims 6 and 8 also invoke a genus of molecules which lack adequate written description.

Regarding the second reagent **R2**, part (d) states that the reagent is used for conducting the second determination of the amount of free thrombin in the reaction mixture (although not explicitly stated in the claim, it is also presumed that the second reagent R2 is also used in step (b) to conduct the first determination). Applicant therefore claims any reagent capable of being used for conducting a determination of free thrombin. The specification fails to adequately identify the claimed genus drawn to all reagents for determining free thrombin.

As examples of second reagents R2, the specification discloses peptidic chromogenic substrates that are acted on by thrombin [0012] as well as antibodies [0009]. See also claims 4 and 5. From the disclosure these two, disparate species of reagents, it is apparent that the genus of second reagents R2 is one that is characterized by substantial variability. However, the disclosure of these two species of second reagents R2 (thrombin substrates that are labeled with a

chromogenic label, and antibodies) fails to adequately to reflect the variation within the claimed genus. The specification does not disclose common structural characteristics of these reagents that are responsible for their function. In this case, the claimed genus is identified only by reference to a functional characteristic (ability to be used to determine free thrombin) and there is no disclosed correlation between structure and function for the members of the genus. As such, the genus of second reagents R2 has not been adequately described because the characteristics that represent the genus are unknown.

In summary, the specification fails to convey evidence of possession of the genus based because the two species disclosed do not sufficiently represent the variability within the genus; one cannot envisage the identities of other members of the claimed genus based on the limited number of species.

For the above reasons, claims 1 and 5-11 lack written description in regards to the claimed genus of "second reagent R2".

Regarding the third reagent **R3**, the claim indicates that this reagent must possess specific functional characteristics, namely the ability to change the conditions of the reaction mixture such that thrombin interacts with AT rather than with the one or more pharmaceutical compounds (thrombin inhibitors) in the sample.

Similarly, claim 6 invokes a genus of "**accelator[s]** of the interaction between AT and the thrombin".

The specification discloses the single example of *heparin* as a reagent possessing the necessary functional characteristics [0014].

This ability of heparin to catalyze the interaction between AT and thrombin was known in the prior art. See, e.g., Triscott et al. (EP 0 927 767 A2, Applicant's IDS of 2/23/2004) at [0002]. However, there is no evidence of record to indicate that other molecules that act to catalyze AT-thrombin interaction in the same manner as heparin were known in the art. The specification does not disclose any partial structural features, chemical properties, or other identifying characteristics shared by the genus of third reagents R3. Further, there is no disclosed correlation between structure and the necessary function (ability to change the conditions of the reaction mixture in the particular manner claimed). Absent a disclosed correlation between structure and function, one skilled in the art would not envisage possession of the genus of reagents based on the disclosure of a single species.

Therefore, while methods involving the use of *heparin* are adequately described (as in instant claim 7), one skilled in the art would not know, based on the specification, what other molecules or compounds might possess the necessary functional characteristics of accelerating or changing the reaction conditions as recited. While it was known in the art that heparin potentiates the antithrombin activity of AT by enhancing the rate of formation of the thrombin:AT complex, this specific example fails to convey evidence of possession of all reagents that act in a similar manner to enhance the interaction of AT with thrombin.

For the above reasons, claims 1, 4, 5-6, and 8-11 lack written description in regards to the claimed genus of "second reagents R2"/ "accelators of the interaction between AT and thrombin".

With respect to claim 8, the genus of "**antagonist[s] for an accelerator of the interaction between AT and thrombin**" is also not adequately described. As discussed above, the genus of "accelerators" lacks adequate written description. As such, the identities of the members of the genus of "antagonists" of such accelerators cannot be envisaged; Applicant is attempting to describe an unknown by reference to another unknown.

Further, although the specification discloses *polybrene* as a reagent that is an antagonist for *heparin,* the specification does not disclose partial structural features, chemical properties, or other characteristics shared by the genus of *antagonists for accelerator of the interaction between AT and thrombin*. One skilled in the art would not know what other reagents besides polybrene might be capable of antagonizing accelerators as required by the claims.

Absent sufficient recitation of distinguishing identifying characteristics, the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

10. Claims 1, 4, and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 recites "determining the amount of **free thrombin**" in the sample-R1 mixture in part (b). Similarly, in step (d) the claim recites "conducting a second determination of the amount of free thrombin in the reaction mixture". However, in step (a) of the claim, it is stated

that the first reagent R1 comprises thrombin and is added to the sample under conditions wherein thrombin interacts with the one or more pharmaceutical compounds in the sample. As such, the claim states that the added thrombin is bound to the pharmaceutical compounds. By contrast, "free" thrombin invokes unbound thrombin. Since the claim conveys in step (a) that thrombin is bound to a pharmaceutical compound(s), the claim is indefinite because it is unclear how "free" thrombin could be determined in steps (b) and (d).

12. Claim 1 recites the limitation "the difference between the first and second determinations" in part (e). There is insufficient antecedent basis for this limitation in the claim.

13. Claims 1, 4, and 6-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: that the sample contains one or more pharmaceutical compounds that inhibit thrombin.

Claim 1 recites that the sample "may" contain one or more pharmaceutical compounds that inhibit thrombin but does not clearly require this (see the preamble). However, the claim later positively recites in step (a) that the sample is mixed with the first reagent under conditions such that thrombin interacts with the one or more pharmaceutical compounds. Because the claim now requires interaction between thrombin and the one or more pharmaceutical compounds, it is essential to the performance of the claimed method that the sample contain such compounds.

14. Claim 9 contains the trademark/trade name Polybrene®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or

trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a specific reagent component and, accordingly, the identification/description is indefinite.

15. Claim 11 recites the limitation "the determination of thrombin". There is insufficient antecedent basis for this limitation in the claim. Claim 1 invokes both a first and second determination of free thrombin. The subsequent reference to "the" determination is therefore ambiguous because it is unclear which determination is being invoked.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1, 4, 6-7, and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. (US 4,219,497) or Philo et al. ("Comparison of antithrombin III assays using biological and chromogenic substrates" Br J Haematol. 1982 Jan;50(1):147-56) in view of Winant et al. (U.S. 5,118,790), Furatu (EP 0 041 366), Morris et al. (US 4,314,987), and Akhavan-Tafti et al. (US 6,068,979).

Plattner et al teach measuring total AT activity by adding excess thrombin (i.e., reagent R1), a chromogenic substrate that is a peptide substrate of thrombin (i.e., second reagent R2),

and heparin (i.e., third reagent R3) and determining free (excess) thrombin via hydrolysis of the chromogenic substrate. See column 6, line 28 to column 7, line 4. Heparin is the same third reagent R3 recited instantly (see claim 7) and would therefore necessarily also possess the same functional characteristics claimed, e.g., the ability to promote interaction of thrombin with AT.

The amount of AT and the amount of color produced from the substrate cleavage by thrombin are inversely proportional, such that the level of AT can therefore be readily determined by monitoring the color development of the reaction mixture (column 6, line 66 to column 7, line 4).

Plattner et al. further teach that this test allows one to measure total AT activity as an entity distinct from the "progressive anti-thrombin activity," which is measured in the absence of heparin. See especially at column 6, lines 52-57.

Thus, the reference teaches determining total AT activity (in which case the measurement occurs in the presence of heparin) as well as progressive anti-thrombin activity (in which case the measurement occurs in the absence of heparin). Both of these measurements are performed by detecting thrombin activity on a chromogenic substrate as instantly claimed.

Plattner et al. differs from the claimed invention in that it fails to specifically teach conducting these two measurements in a single reaction mixture. In other words, Plattner et al. teach performing the claimed determination steps *in parallel*, while the instantly claimed invention requires that they be performed *sequentially*, on the same sample or reaction mixture.

In addition, Plattner et al. is silent as to whether the sample may contain one or more pharmaceutical compounds that inhibit thrombin.

Like Plattner et al., Philo et al. similarly teach methods of measuring antithrombin III levels in plasma samples by incubating samples with thrombin (i.e., reagent R1), either with or without heparin (i.e., reagent R3). See the abstract. The methods also employed the colorimetric thrombin substrate S-2238 (i.e., reagent R2). See page 148, "Materials and Methods". Similar to the methods of Plattner et al., Philo et al. teach two measurements: a first determination of "progressive anti-thrombin" by adding thrombin (i.e., first reagent R1) to plasma samples (see the abstract and page 149, "Progressive antithrombin assays) and determining free thrombin by adding the colorimetric thrombin substrate S-2238 and measuring the resulting absorbance over time (see also at page 148, "Materials and Methods"); and a second determination of "heparin cofactor" in which heparin is also added to the reaction mixture (pages 149-152, see especially at page 149, "Heparin co-factor assays").

Like Plattner et al., the teachings of Philo et al. also differ from the claimed invention in that the reference performs the above two measurements in *parallel*, using multiple aliquots of the plasma samples (abstract). The reference therefore fails to specifically teach subjecting the same sample to both determinations in *sequence*.

In addition, Philo et al. is silent as to whether the sample may contain one or more pharmaceutical compounds that inhibit thrombin.

Winant et al. teach the thrombin inhibitor hirudin, which is an effective anticoagulant and antithrombolytic agent that may be used in treatment of antithrombin-III deficiency and other conditions (i.e., pharmaceutical compound that inhibits thrombin). See column 1, lines 10-25.

The teachings of Winant et al. establish that antithrombin-III deficiency was a known medical condition that may be treated with the thrombin inhibitor hirudin.

It would have been obvious to one of ordinary skill in the art to use the methods of measuring antithrombin III of Plattner et al. or Philo et al. in order to measure antithrombin III in samples taken from individuals being treated with hirudin for antithrombin-III deficiency. One would be motivated to do this in order to assess or monitor the status of disease, i.e. to determine whether hirudin is effectively treating the antithrombin-III deficiency. Put another way, it would have been obvious to use known methods of measuring antithrombin III (such as those of Plattner et al. or Phil et al.) in a clinical context in order to study diseases associated with alterations in antithrombin III. Because individuals afflicted with antithrombin III deficiency were known to be treated with hirudin, when assessing such individuals it would have been obvious to arrive at the claimed invention by assessing antithrombin III in samples from such individuals as they would contain this thrombin inhibitor.

With respect to the recitation that thrombin does not initially interact with AT until after addition of third reagent R3, such features are considered to reflect intrinsic physiological properties of the thrombin-antithrombin III-heparin system. As such, when assaying antithrombin III in individuals under treatment with hirudin, it is presumed that added thrombin would initially interact with hirudin prior to heparin addition as claimed.

Regarding the determinations of thrombin twice in single reaction mixture, it was known in the art to subject a single sample to multiple measurements in sequence. For example, Furatu et al. teach subjecting a sample to a plurality of reactions sequentially (see especially pages 1-4). In one embodiment, a reagent solution containing an enzyme is added to a sample solution to cause enzyme reaction, and the result is determined by colorimetric detection (page 3, the first

paragraph). Next, a second reagent solution is added to the first reagent solution and a second detection step is performed (page 3, the last paragraph to page 4, first paragraph).

Furatu et al. teach that one advantage in performing a plurality of measurements on a single sample is that only a very small amount of a sample is used, which decreases the sampling number and omits the need for successive sampling operations (page 2).

Morris et al. teach performing a continuous sequence of tests in time on the same blood sample in order to avoid numerous errors that may be introduced by delays in time, differences in blood samples, etc. (column 3, lines 32-53).

Akhavan-Tafti et al. teach that it is frequently desirable to be able to detect and/or quantify more than one analyte at a time in a single test system; savings in time, reagents and materials can thereby be realized and assay protocols can be simplified (column 1, lines 55-63). The solution proposed by Akhavan-Tafti involves sequential detection (see especially the title and abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to detect thrombin activity in the absence and in the presence of heparin as taught by Plattner et al. or Philo et al. and Winant et al., but to perform these two measurements *sequentially* in the same reaction mixture rather than in parallel. Performing multiple measurements on a single sample was known in the art, as taught for example by Furatu et al., Morris et al., and Akhavan-Tafti et al. Although these references do not relate to determination of AT-III specifically, given that the chemistry of AT-III/thrombin reaction were well established at the time of the invention (as taught for example in Plattner et al. and Philo et al.), it would have been further obvious to perform the measurement of "progressive anti-thrombin activity" in the absence of heparin first,

and to then add heparin for determination of total AT-III activity (thereby changing the reaction conditions as recited). Put another way, it would have been obvious to use known techniques to improve upon known methods in which multiple measurements are performed, such as those of Plattner et al. and Philo et al.

One would be motivated to perform the measurements sequentially on a single sample in order to minimize the amount of sample required, in order to save time, reagents, and materials, in order to simplify assay protocols, and/or in order to reduce errors due to delays in time and/or differences in blood samples.

With respect to claim 11, Plattner et al. teach determining thrombin by monitoring color development of the reaction mixture as a function of time, i.e. a kinetic determination (column 6, line 66 to column 7, line 4; see also at column 5, lines 43-51). Philo et al. similarly teach measuring the absorbance of the mixture over time (page 149).

18. Claims 8-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Plattner et al. or Philo et al. in view of Winant et al., Furatu, Morris et al., and Akhavan-Tafti et al. as applied to claim 1 above, and further in view of Exner (US 6,051,434).

The Plattner et al., Philo et al., Furatu, Morris et al., and Akhavan-Tafti et al. references are as discussed above. Plattner et al. fail to specifically teach that the first reagent R1 also comprises polybrene.

Exner teaches a mixture including polybrene, in order to reverse the effect of any heparin that may be present in test samples. See column 3, lines 34-37. Plattner et al. and Philo et al. teach how determinations of progressive antithrombin are performed in the absence of heparin.

Therefore, when determining AT according to the prior art methods as discussed above, it would have been further obvious to one of ordinary skill in the art at the time of the invention to include polybrene, as taught by Exner, in the step of measuring the progressive anti-thrombin activity, in order to control for the effect of any heparin that may be present in test samples.

More particularly, as this measurement step of Plattner et al. and Philo et al. requires determining the activity of anti-thrombin in the absence of heparin, the inclusion of polybrene would ensure the success of the assay, thereby providing motivation to combine Plattner et al and Exner references. In addition; one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in including the polybrene of Exner in the method of Plattner et al. or Philo e tal. Furatu, Morris et al., and Akhavan-Tafti et al., since Plattner et al. and Philo et al. each teach measurement steps excluding thrombin:AT-III interaction, and the polybrene of Exner is well known in the art as capable of preventing the effect of heparin on inducing thrombin:AT-III complexes.

Response to Arguments

19. Applicant's arguments filed 3/18/2009 have been fully considered.

20. With respect to the rejections under § 112, 1st paragraph (written description), Applicant points to the instant amendments to the claims (Reply, pages 4-5), which are not found persuasive to obviate the rejections for reasons of record as set forth above.

Applicant further argues with respect to claim 6 that it is well known that other variables were known to accelerate thrombin-AT reaction (Reply, page 5, first full paragraph). This is not found persuasive because the arguments of counsel cannot take the place of evidence in the

record; Applicant has not advanced evidence or pointed to any evidence already of record to show that accelerators of the thrombin-AT interaction were well known in the art at the time of the instant invention. In addition, Applicant is claiming an accelerator as a component of the first reagent R1. Thus, the genus of accelerators claimed encompasses a large variety of molecules possessing the same functional characteristics as heparin. However, the specification does not describe what other molecules would act in the same way as heparin. For all of these reasons, it is maintained that the genus of "accelerators" is not adequately described.

Applicant further argues with respect to claim 8 that those skilled in the art will be able to identify antagonists for the accelerator (Reply, page 5, second full paragraph). This is not found persuasive because the written description requirement is separate and distinct from the enablement requirement. Here, Applicant points to as-yet discovered reagents, the structures of which cannot be envisaged by the skilled artisan. With the exception of Polybrene, the specification does not describe with particularity any other reagents that would possess the necessary functional characteristics.

21. With respect to the rejections under § 103 as being unpatentable over Plattner et al. in view of Furatu, Morris, and Akhavan-Tafti et al., Applicant argues one skilled in the art would not have expected that it would have been possible to obtain an accurate determination of AT by conducting two determinations of free thrombin successively in one and the same sample (Reply, pages 5-6).

This is not found persuasive because whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed.

Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035, 206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007).

Furthermore, any objective evidence should be supported by an appropriate affidavit or declaration in order to be of probative value. See MPEP 716.01(c). In the instant case, the general arguments of counsel are unsupported by an appropriate affidavit or declaration and do not constitute sufficient evidence to establish the presence of unexpected results.

Applicant further argues that none of the cited art teaches the measurement of free thrombin twice in the same sample under different conditions (Reply, pages 6-7).

This is not found persuasive because "[t]he test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

In the instant case, from the teachings of Furatu, Morris, and Akhavan-Tafti et al., it is evident that those of ordinary skill in the art appreciated the advantages of performing multiple *measurements* on a single sample. It would have been obvious to combine such teachings with those of Plattner et al., in which multiple measurements of thrombin activity were conducted (albeit on different samples), by performing the multiple measurements of thrombin activity in a single sample. One would have been motivated to combine the reference teachings in this manner because performing multiple measurements on a single sample was known in the art to

save time, reagents, and materials, simplify assay protocols, and/or in order to reduce errors due to delays in time and/or differences in blood samples.

Applicant further argues for evidence of long-felt need (Reply, pages 7-8). This is not found persuasive because initially, any objective evidence should be supported by an appropriate affidavit or declaration in order to be of probative value. See MPEP 716.01(c).

Further, establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. See MPEP 716.04.

In the instant case, Applicant points to a post-filing publication by Hickey as evidence of long-felt need. However, since the Hickey article was published in 2008, it fails to establish evidence of long-felt need.

With respect to the rejections of claims 8-9, Applicant further argues that it would not be obvious to use polybrene in the step of measuring progressive anti-thrombin activity because in Plattner, this step is conducted in the presence of heparin (Reply, page 8). This is not found persuasive because Plattner makes clear that measurement of progressive anti-thrombin activity is conducted in the absence of heparin (column 6, lines 53-55).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The

examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641